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(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)* : KILLEN, Christopher, Robert, James [GB/GB]; SmithKline Beecham Pharmaceuticals, Clarendon Road, Worthing, West Sussex BN14 8QH (GB).

(74) Agent: JONES, Pauline; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).

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(54) Title: PREPARATION OF 2-AMINO-6-CHLOROPURINE

(57) Abstract

A process for preparing 2-amino-6-chloropurine comprises reacting a 2,9-diacylated derivative of guanine with a chlorinating agent in the presence of a phase transfer catalyst containing chloride ions, and thereafter removing the 9-acyl group and the 2-acyl group by hydrolysis.

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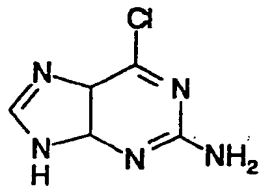
Preparation of 2-amino-6-chloropurine

This invention relates to a process for the preparation of a compound useful as an intermediate in the preparation of pharmaceutical compounds.

The compound 2-amino-6-chloropurine of formula (I):



(I)

is a useful intermediate in the preparation of nucleoside analogue antiviral agents, such as penciclovir and famciclovir, described in EP-A-141927 (Example 1) and EP-A-182024 (Example 2). The intermediate is 9-substituted with an appropriate side chain precursor, followed by conversion of the 6-chloro moiety to a hydroxy (a guanine) or hydrogen (a 2-aminopurine).

EP-A-203685 (Beecham Group p.l.c.) describes a process for preparing a compound of formula (I) as hereinbefore defined, which process comprises reacting guanine with a chlorinating agent in the presence of a phase transfer catalyst containing chloride ions. EP-A-433846 (Hoechst Aktiengesellschaft) describes a corresponding process for preparing the 2-acylated derivative, involving chlorination of 2,9-diacylguanine and subsequent removal of the 9-acyl group by hydrolysis.

The reaction is preferably carried out in a polar inert organic solvent such as acetonitrile, tetrahydrofuran, dioxan, nitromethane, diglyme, dimethoxyethane, or dichloromethane. Acetonitrile is highly preferred.

Suitable phase transfer catalysts include tetrasubstituted ammonium chlorides. Examples of ammonium substituents include C_{2-12} alkyl, usually C_{2-4} alkyl, or phenyl or benzyl. Other possible phase transfer catalysts include tetra-substituted phosphonium chlorides wherein examples of the substitutents are as defined above for ammonium chlorides. Preferably the phase transfer catalyst is tetraethylammonium chloride.

The phase-transfer catalyst is preferably present in an amount of from 1 to 3 equivalents of the compound of formula (II) and preferably from 1 to 2 equivalents.

A preferred chlorinating agent is phosphorus oxychloride.

Preferably the chlorinating agent is present in an amount of from 2-10 preferably from 3-6 molar equivalents of the guanine derivative.

The reaction may be effected in the presence of a weak base, such as a tertiary amine, for example N,N-dimethylaniline or diethylaniline or triethylamine. The base is usually present in an approximately molar equivalent amount with respect to the guanine derivative. Alternatively, a catalytic amount of water may be added to the reaction mixture. When acetonitrile is the solvent, added base may not be necessary, but is preferred.

The reaction is preferably carried out at an elevated temperature of from 30-100^{o}C, most preferably under reflux and/or with ultrasonication at 50-70^{o}C.

Preferably the reaction is allowed to proceed for a period of greater than half an hour, usually less than 30 hours.

We have now discovered that the compound of formula (I) may be prepared from 2,9-diacylguanine.

Accordingly, the present invention provides a process for preparing 2-amino-6-chloropurine, which process comprises reacting a 2,9-diacylated derivative of guanine with a chlorinating agent in the presence of a phase transfer catalyst containing chloride ions, and thereafter removing the 9-acyl group and the 2-acyl group by hydrolysis.

The reaction is described in EP-A-203685 and EP-A-433846, which are incorporated herein by reference, except that methyltriethylammonium chloride is a preferred phase transfer catalyst; the amount of phosphorus oxychloride may be reduced to 2-4 equivalents, and the reaction time can be reduced.

If the removal of the 9-acyl group generally occurs at ambient temperature (below 30°C), but higher temperatures and reaction times (80-100°C, 1-2 hours) are needed for removal of the 2-acyl group. Aqueous sodium hydroxide is a suitable basic medium for the hydrolysis.

The following example illustrates the invention.

Example

Diacetyl guanine (8.0g, 0.034 moles), triethylmethylammonium chloride (15.45g, 0.102 moles), and triethylamine (4.74 mls, 0.034 moles) were heated together with stirring in acetonitrile (70mls) to 50°C. Phosphorus oxychloride (6.34 mls, 0.068 moles) was then added and stirring continued for 4 hours. The reaction mixture was cooled and then added to aqueous sodium hydroxide solution (20g in 300mls water). The reaction mixture was heated to 80°C for 2 hours and then the volume made up to 300 mls with water. The mixture was cooled to 25°C and the pH adjuster to 7 using 10% hydrochloric acid. The resulting slurry was stirred for fifteen minutes and the product filtered off and washed with water 30 mls and then dried at 80°C under vacuum to give a cream/off white coloured product.

Weight 2-amino-6-chloropurine 4.69 g (74.6% yield).

Claims

1. A process for preparing 2-amino-6-chloropurine, which process comprises reacting a 2,9-diacylated derivative of guanine with a chlorinating agent in the presence of a phase transfer catalyst containing chloride ions, and thereafter removing the 9-acyl group and the 2-acyl group by hydrolysis.

2. A process according to claim 1, as described in EP-A-203685 and EP-A-433846.

3. A process according to claim 2, wherein the chlorinating agent is phosphorus oxychloride and the phase transfer catalyst is methyltriethylammonium chloride.

4. A process according to in claim 3, wherein the amount of phosphorus oxychloride is 2-4 equivalents with respect to the 2,9-acylated guanine.

5. A process according to claim 1, wherein aqueous sodium hydroxide is used as the basic medium for the hydrolysis.

6. A process according to claim 1, substantially as described herein with reference to the Example.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/00185

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D473/40

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0 433 845 (HOECHST) 26 June 1991 *Complete specification*	1-6
A	EP,A,0 203 685 (BEECHAM) 3 December 1986 cited in the application *Complete specification*	1-6
A	EP,A,0 433 846 (HOECHST) 26 June 1991 cited in the application *Complete specification*	1-6
P,A	WO,A,9 213 859 (SMITH-KLINE BEECHAM) 20 August 1992 *Complete specification*	1-6

° Special categories of cited documents :[10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
21 APRIL 1993	13. 05. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	LUYTEN H.W.

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300185
SA 69726

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82